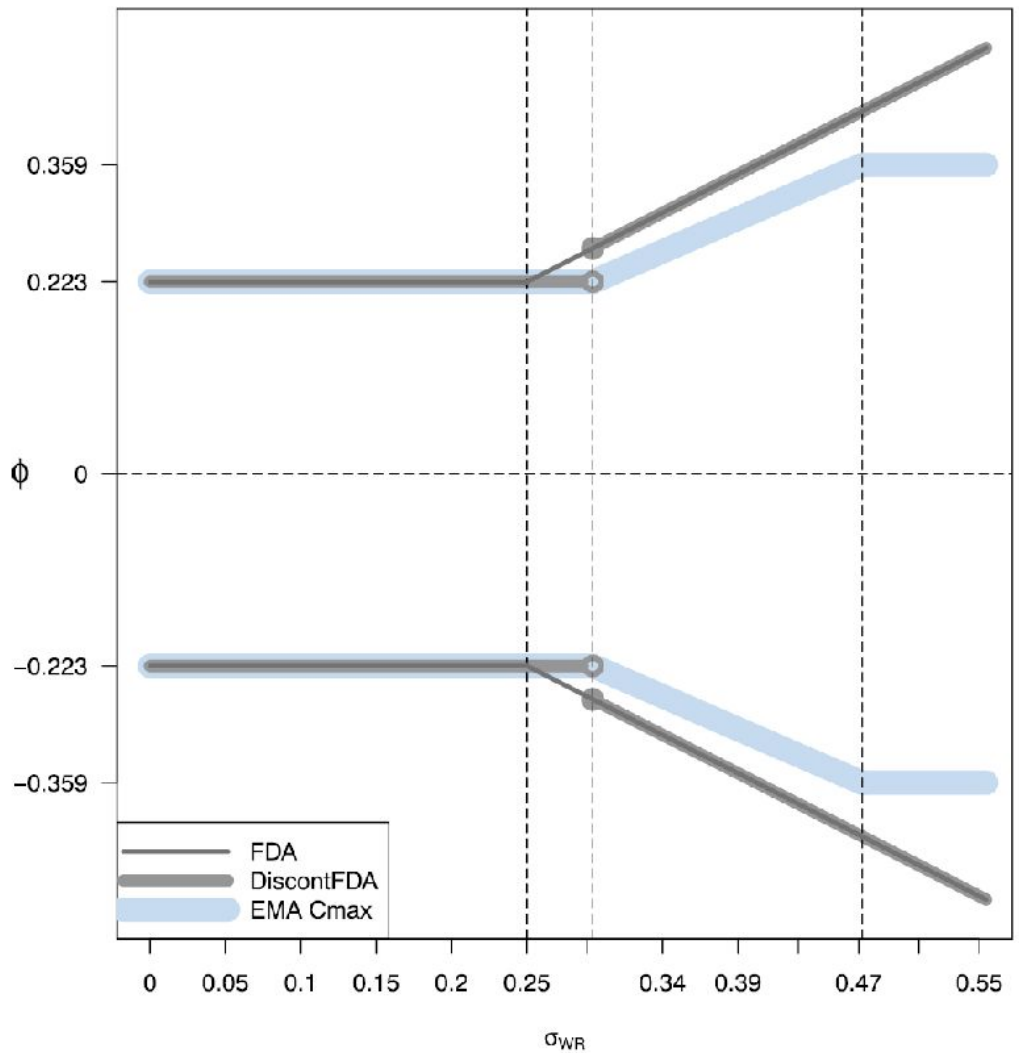
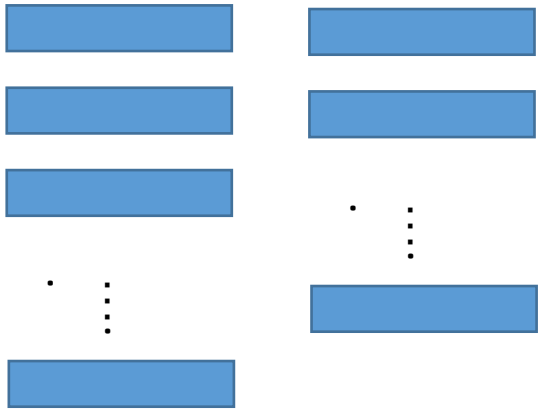


FIGURE 1 Bioequivalence limits according to the EMA[4] and the FDA[5] regulations, scaled according to the within-subject variability of the reference R formulation, σ_{WR}. In the EMA regulation, scaling starts at $\sigma_{WR} = 0.294$ ($CV_{WR} = 30\%$) and ends at $\sigma_{WR} = 0.472$ ($CV_{WR} = 50\%$). In the FDA regulation, scaling continues indefinitely from its starting point. There are two possible interpretations of the FDA regulation: In one of them (labelled here as FDA) scaling starts at $\sigma_{WR} = 0.25$ ($CV_{WR} = 25.4\%$); in the other (DiscontFDA) scaling starts at $\sigma_{WR} = 0.294$. A true condition of bioequivalence holds if the true but unknown formulation effect value, ϕ, lies between these limits. The scaled limits refer to *Cmax* and *AUC* in the FDA regulation and only to *Cmax* in the EMA regulation, both of which are considered in logarithmic scale

L1: Metabolites list 1

L2: Metabolites list 2



Statistical comparison (e.g., equivalence test) with some biological meaning

Metabolic pathways database (metabolites which are involved in them), e.g., KEGG

ORA analysis: pathway $i = 1, \ldots, n$ "overrepresented" in L1, L2?

Main problem: dependency between paths

	Path1	Path2	Path3	Path4	Path5	Path6	...	Pathn
L1	FALSE	FALSE	FALSE	TRUE	TRUE	FALSE	...	FALSE
L2	TRUE	FALSE	TRUE	TRUE	FALSE	FALSE	...	TRUE